PATENT
459050-2000.1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Evan Harris WALKER et al.
Serial No.	:	10/766,575
Filed	:	January 27, 2004
Title	:	HIGH SPECIFICITY ANTICANCER DRUG DESIGN PROCESS
Group Art Unit	:	1614
Examiner	:	Lambkin, Deborah C.

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Deborah L. Lu, Reg. No. 50,940
Name of Applicant, Assignee or Registered Representative

Deborah L. Lu
Signature

28 March 2006
Date of Signature

DECLARATION UNDER 37 C.F.R. § 1.132

Mail Stop **Amendment**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Eduardo Palomino, declare and state that:

1. I make this declaration in connection with U.S. application Serial No. 10/766,575. I am familiar with its prosecution history, particularly the Office Action mailed on October 28, 2005.

2. Attached is my Curriculum vitae. In view of my education, training and experience, I consider myself qualified to express the opinions stated herein.

3. The Examiner alleges that the specification is enabling for the examples specifically described therein, but does not reasonably provide enablement for all and any substance that may or may not meet the criteria recited in the claims. More specifically, the Examiner alleges that one of ordinary skill in the art would have to experiment unduly to determine which compounds or substances beyond the examples given would work as "a substantially biologically inert proto-drug", "a substantially inert activation drug", "a differentially selective moiety", "a toxic moiety", "a cap moiety" and "substantially inert activation drug".

4. The presently claimed invention is directed to anticancer drug design comprising a cytotoxic substance or anticancer agent known in the art, for which a basic mechanism of action is known. Such anticancer agents comprise a wide range including nitrogen mustards, podophyllotoxins, antimetabolites, intercalating agents, synthetic hormones, taxols, and others with specific or general toxicity. The presently claimed invention is also directed to substances with tissue selectivity, whereby the differentially concentrating moiety may belong to a wide range of groups such as the benzophenothiazines, the benzoporphyrins including hematoporphyrin, the Nile Blue series of dyes, pyrimidopyrimidines such as dipyridamole, the vitamins E and A series of compounds, the thioxanthones, and others with specific selectivity for a variety of animal tissues. The presently claimed invention is also directed to a cap moiety which may belong to several groups of compounds including protecting groups such as the silanes and siloxanes, ethers such as glucosides, esters such as glucuronides and others that block the toxicity of the substance. The presently claimed invention is also directed to substances that act as activators to release the toxic compound. The activation drug may belong to several groups including but not limited to compound classes such as the fluorides, enzymes such as glucosidase and glucuronidase, and others with similar specificity for the cap moiety chosen. As as is clear from the foregoing, one of ordinary skill in the art, exercising reasonable curiosity, would learn from a modest search of the relevant art, cytotoxic substances or anticancer agents, substances with tissue selectivity, caps and activators based upon the teaching of the specification.

5. A "substantially biologically inert proto-drug" is clearly defined on page 5 of the specification as originally filed. According to the specification, the assemblage is herein defined as a complex proto-drug and activation drug system which includes one or more differentially selective moieties, one or more toxic moieties and one or more moieties that serve the purpose of providing a "mask" or "cap" to the toxic moieties. Drugs performing this function are known to, and can easily be identified by one of ordinary skill without undue experimentation, consistent with the general examples of paragraph # 4.

6. A "substantially inert activation drug" is clearly defined on pages 5-6 of the specification as originally filed. According to the specification, an activation drug is defined as one or more chemicals serving the function of activating the proto-drug of the assemblage. Drugs performing this function are known to, and can easily be identified by one of ordinary skill without undue experimentation. Moieties performing this function are known to, and can easily be identified by one of ordinary skill without undue experimentation, consistent with the general examples of paragraph # 4.

7. A "differentially selective moiety" is clearly defined on page 7 of the specification as originally filed. According to the specification, a differentially selective moiety or moieties (also referred to as the "differentially concentrating moiety") of a chemical compound has properties such that the compound will differentially concentrate in cancer tissues as compared with normal tissues of the treated body whether in animals or people. Moieties performing this function are known to, and can easily be identified by one of ordinary skill without undue experimentation, consistent with the general examples of paragraph # 4.

8. A "toxic moiety" is clearly defined on page 7 of the specification as originally filed. According to the specification, a toxic moiety or moieties of a chemical compound has properties such that the compound will be capable of killing the cells or tissues wherein it is concentrated. Moieties performing this function are known to, and can easily be identified by one of ordinary skill without undue experimentation, consistent with the general examples of paragraph # 4.

9. A "cap moiety" is clearly defined on pages 7-8 of the specification as originally filed. According to the specification, a mask or cap moiety or moieties of a chemical compound has properties such that the proto-drug's toxicity will not be expressed, that is to say, not act as a toxin in the cell or in the tissue where it is located, until the proto-drug is activated by the

application or administration of the activation drug. The term mask or cap moiety is herein defined to be any modification in the proto-drug serving to mollify or eliminate the toxicity of the overall compound whereby such cap is later removed or modified by the activation drug. The term mask or cap need not be, and is not limited to being, a chemical moiety that literally covers, or is chemically bonded directly to the toxic moiety or to the toxic site of the proto-drug. Moieties performing this function are known to, and can easily be identified by one of ordinary skill without undue experimentation, consistent with the general examples of paragraph # 4.

10. "Substantially inert" is clearly defined throughout the specification (see, e.g., pages 4, 6, 8, 9 and 21) as originally filed. According to the specification, substantially inert means having no toxic or little effect on the body when administered alone.

11. The terms "a substantially biologically inert proto-drug", "a substantially inert activation drug", "a differentially selective moiety", "a toxic moity", "a cap moiety" and "substantially inert" are definite and adequately supported in the instant specification such that one of ordinary skill in the art would know where to search for known compounds in the art and ascertain the metes and bounds of the compounds that fall within the purview of the claims without undue experimentation, consistent with the general examples of paragraph # 4.

12. All statements made herein of my own knowledge are true and all statements made on information believed to be true. These statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 3/15/06

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EDUCATION

B.S. Chemistry and Pharmacy 1974, National University, Bogota, Colombia
Thesis: Psidium Caudatum: Phytochemical Studies.
M.S. Organic Chemistry 1983, Wichita State University, Wichita, KS.
Thesis: Ring Expansion of Aziridinones.
Ph.D. Organic Chemistry 1986, Wayne State University, Detroit, MI.
Dissertation : Electron Transfer Photooxygenation of Sterically Strained Heterocycles.
Minor: Analytical Chemistry.

EXPERIENCE

1991- Research and Natural Products. Walker Cancer Research Inst. Detroit, MI
Design, synthesis and in-vitro/in-vivo evaluation of new anticancer agents. Evaluation, isolation and characterization of anticancer and antiviral agents from natural products(plants). Development of methods for biological testing.

1992-02 Lecturer (PT) Wayne State University Detroit, MI
Teaching of General Chemistry at all levels, Organic and Bioorganic Chemistry .

1986-90 Researcher and postdoctoral fellow. Michigan Cancer Foundation, Detroit, MI
Synthesis of new nucleosides analogues as anti-AIDS agents. Synthetic modifications of steroids as probes to map receptor characteristics in breast cancer. Computer-aided molecular modeling in drug design.

1981-85 Graduate Research Assistant Wayne State University and Wichita State University
Research in Synthetic Organic Chemistry and Photochemistry. New methods for the synthesis of oxiranes, aziridines and peroxides. Extensive use of analytical intrumentation (NMR, Fluorimetry, GC, HPLC, UV, IR, etc.).

1975-80 Director Social Security Pharmacy. Bogota, Colombia

Management of personnel and drugstores. Compilation of drug standards.

PARTIAL LIST OF PUBLICATIONS

Schaap, P; Palomino E. The Photochemical Preparation of Ozonides by Electron - Transfer Photo-Oxygenation of Epoxides. Tetrahedron., 41, 2229, 1985.

Talaty, E.; Palomino, E. et al. Reaction of Aziridinones with Thiourea: A Novel Synthesis of Specifically Substituted Glycocyamidines and Hydantoins. Synth. Comm 17(9), 1063,1987.

Palomino, E.; Kessel, D.; Horwitz, J. P. A Dihydropyridine Carrier System for Sustained Delivery of 2',3'-Dideoxynucleosides to the Brain. J. Med. Chem. 32, 622, 1989.

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Hazeldine, S.T, Polin, L.A, Kushner, J, White, K, Bouregeois N.M, Crantz, B, Palomino, E, Corbett, T, Horwitz, J.P. II. Synthesis and biological evaluation of some bioisosteres and congeners of the antitumor agent, 2-{4-[(7-chloro-2-quinoxalinyl)oxy]phenoxy} propionic acid (XK469) J. Med. Chem. 45, 3130-3137, 2002.

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